Izvorni znanstveni članak | Original scientific paper

Uzroci povišenog troponina u bolesnika s urednom koronarografijom

Causes of Elevated Troponin in Patients with Normal Coronary Angiography

Ana Reschner Planinc,
Maja Strozzi*,
Zoran Miovski,
Kristina Marić Bešić,
Joško Bulum

Medicinski fakultet Sveučilišta u Zagrebu, Klinički bolnički centar Zagreb, Zagreb, Hrvatska
University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

SAŽETAK: Porast troponina u većini slučajeva upućuje na oštećenje stanica miokarda, no povišene vrijednosti troponina nisu uvijek posljedica infarkta ili ishemije. Svrha je ovog istraživanja bila osvijetliti različite uzroke povišenoga troponina u bolesnika s normalnim nalazom koronarografije. U Kliničkom bolničkom centru Zagreb 2014. godine izdvojeno je 947 bolesnika iz baze podataka Laboratorija za invazivnu kardiologiju, u kojih je učinjena koronarografija radi postavljanja dijagnoze akutnoga koronarnog sindroma (ACS). Trideset dva bolesnika (3,38 %) nisu imala uzrok oštećenja miocita od koronarne bolesti srca (CAD), definiranoj kao stenoza lumena koronarnih arterija veća od 30 %. Porast miokardnoga troponina T (cTnT) u bolesnika s normalnim koronarnim arterijama rezultat su različitih uzroka, uključujući hipertenzivnu bolest srca, Takotsubo sindrom, supraventrikulsku tahikardiju, miokarditis i dilatativnu kardiomiopatiju, da spomenemo samo neke. Osim u ACS-u, cTnT može biti povišen u nizu različitih stanja, o čemu treba razmišljati kada se razmatra klinička slika, i to može biti odraz nekroze miokarda i u odsutnosti značajne CAD.

SUMMARY: Troponin elevation usually indicates myocardial cell injury. However, elevated values of troponin are not always a consequence of infarction or ischemia. The aim of this study was to elucidate the diverse etiologies of elevated troponin in patients with normal coronary angiography. There were 947 patients at the Zagreb University Hospital Centre identified from the catheterization database who underwent coronary angiography in 2014 due to suspected acute coronary syndrome. We identified 32 (3.38%) patients who had an alternative cause for myocyte injury other than coronary artery disease, defined as coronary artery lumen stenosis above 30%. The elevation of cardiac troponin T (cTnT) in patients with normal coronary angiography was found to be the consequence of diverse etiologies, including hypertensive heart disease, Takotsubo syndrome, supraventricular tachycardia, myocarditis, and dilated cardiomyopathy, to name a few. Apart from acute coronary syndrome, cTnT can be elevated in a number of different conditions, which should be considered according to clinical presentation, and that could still reflect myocardial necrosis even in the absence of significant coronary artery disease.

KLJUČNE RIJEČI: troponin, koronarna bolest srca, normalan nalaz koronarografije, oštećenje stanica miokarda.

KEYWORDS: cardiac troponin, coronary artery disease, normal coronary angiography, myocardial cell injury.

CITATION: Cardiol Croat. 2019;14(7-8):159-66. | https://doi.org/10.15836/ccar2019.159

***ADDRESS FOR CORRESPONDENCE**: Maja Strozzi, Klinički bolnički centar Zagreb, Kišpatićeva 12, HR-10000 Zagreb, Croatia. / Phone: +385-98-233-650 / E-mail: maja.strozzi@gmail.com

ORCID: Ana Reschner Planinc, http://orcid.org/0000-0002-6723-6822 • Maja Strozzi, http://orcid.org/0000-0003-4596-8261 Zoran Miovski, http://orcid.org/0000-0002-3850-8905 • Kristina Marić, Bešić, http://orcid.org/0000-0002-4004-7271 Joško Bulum, http://orcid.org/0000-0002-1482-6503

TO CITE THIS ARTICLE: Rechner Planinc A, Strozzi M, Miovski Z, Marić Bešić K, Bulum J. Causes of Elevated Troponin in Patients with Normal Coronary Angiography. Cardiol Croat. 2019;14(7-8):159-66. | https://doi.org/10.15836/ccar2019.159

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2019.159

RECEIVED:
May 29, 2019
UPDATED:
June 11, 2019
ACCEPTED:
July 1, 2019

Uvod

Troponin je strukturna komponenta sarkomere i sastoji se od triju proteina: troponin C (cTnC), troponin I (cTnI) i troponin T (cTnT), te kontrolira mišićne kontrakcije skeletnih mišića i miokarda, odgovarajući na prisutnost intracelularnog kalcija. Približno 6 – 8 % cTnT-a te 2,8 – 8,3 % cTnI-a nađeno je u citosolu[1]. Najčešće se

Introduction

Troponin is a structural component of sarcomere and consists of three proteins: troponin C (cTnC), troponin I (cTnI), and troponin T (cTnT), which control skeletal and cardiac muscle contraction in response to intracellular calcium. Approximately 6-8% of cTnT and 2.8-8.3% of cTnI are found floating free in the cytosol[1].

oslobađaju kao rezultat proteolitičke degradacije. Neposredno nakon oštećenja miocita troponin se oslobađa iz citoplazme, a slijedi oslobađanje većih količina vezanih za miofilamente koji propadaju.[2]

Mjerenje cTnI-a i cTnT-a u serumu superiorno je, u usporedbi s mjerenjem cTnC-a, u identifikaciji oštećenja srčanog mišića u smislu senzitivnosti i specifičnosti mjerenja miokardnih enzima[1]. Nakon oštećenja miokarda potrebna su 3 - 4 sata da cTnT počne rasti u perifernoj krvi, a njegova koncentracija ostaje povišena 10 – 14 dana.[3] Troponini su markeri prisutnosti oštećenja stanica miokarda i njihove nekroze, ali ne upućuju na mehanizam koji ga uzrokuje.[4-7]

Godine 2019. Europsko kardiološko društvo objavilo je četvrtu Univerzalnu definiciju infarkta miokarda (MI), koji definira 5 tipova. Pojam MI treba koristiti u slučajevima akutnog oštećenja miokarda s kliničkim dokazima akutne ishemije s porastom ili padom vrijednosti cTnT-a te minimalno jednim od sljedećeg: simptomi ishemije miokarda, novonastale promjene u EKG-u, razvoj patološkog Q-zupca, slikovnim metodama potvrđen novi gubitak vijabilnog miokarda ili novi ispad regionalne kontraktilnosti koji se može povezati s ishemijom te identifikacija koronarnoga tromba angiografijom ili autopsijom (ne vrijedi za tip 2 i 3). Klasičan MI, kao posljedica opstruktivne koronarne bolesti srca (CAD), klasificiran je kao tip 1 MI-ja. Tip 2 ispunjava navedene kriterije, osim opstruktivne CAD, i karakterizira ga disproporcija između opskrbe i potrebe miokarda za kisikom[8]. Stoga MI treba dijagnosticirati u povezanosti s kliničkom slikom, elektrokardiografskim promjenama itd. Posljednjih se godina spominje pojam MINOCA (*Myocardial Infarction with NON-obstructive coronary arteries*), ili MI s neopstruktivnim koronarnim arterijama, koji privlači sve više pozornosti i smatra se da obuhvaća i do 8 % bolesnika s MI-jem.

Dokaz povišenog cTnT-a, bez gore spomenutih dodatnih kriterija za MI, treba nazvati samo oštećenjem miokarda. Ono može biti rezultat mnogih kliničkih stanja kardiološke ili nekardiološke etiologije[9-11], koja su navedena u **tablici 1** i objašnjena u kasnijem tekstu.

Most commonly they are released as a result of proteolytic degradation. After cardiomyocyte injury, troponin is initially released from the cytoplasmic pool, followed by release from quantities bound to deteriorating myofilaments[2].

The measurement of serum cTnI and cTnT is superior in comparison with the measurement of cTnC in the identification of cardiac muscle damage in terms of sensitivity and specificity to cardiac muscle enzyme measurements[1]. In peripheral blood, it takes 3-4 hours for cTnT to begin to rise after the onset of myocardial injury, and its concentration remains increased for 10-14 days[3]. Troponins are markers which indicate presence of myocardial cell injury and necrosis but do not indicate the mechanism causing it[4-7].

In 2019, the European Society of Cardiology published the Fourth Universal Definition of Myocardial infarction that defines 5 types of myocardial infarction. The term myocardial infarction (MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia with detection of a rise and/or fall of cTnT values, and at least one of the following: symptoms of myocardial ischemia, new ischemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, or identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs). Classical MI as a consequence of obstructive coronary artery disease (CAD) is classified as type 1 MI. Type 2 MI fulfils the abovementioned criteria besides obstructive CAD, and is evidenced by an imbalance between myocardial oxygen supply and demand[8]. Therefore, MI should be diagnosed in conjunction with other supportive evidence, such as corresponding clinical presentation, electrocardiographic changes, etc. In the last years, the term MINOCA (Myocardial Infarction with NON-obstructive coronary arteries), has received much attention, and it is thought that up to 8% of patients with MI actually have MINOCA.

TABLE 1. Possible etiologies of elevated troponin in patients with normal coronary angiography[13-27].

Direct damage to myocardium	Diminished oxygen supply to myocardium	Increased oxygen demand	Increased demand and diminished supply	Other causes
Inflammation (myopericarditis)	Coronary embolus	Left ventricular hypertrophy	Tachycardia, severe AS	Infiltrative disease of myocardium
Electrical discharge	Shock of various etiologies	Cardiomyopathy	Tachycardia associated with bleeding	Renal failure
Mechanical damage	Gastrointestinal bleeding	COPD	Sepsis	Hypothyroidism
Chemical damage	Anemia	Valvular lesions (regurgitant or stenotic)	Severe CHF	False positive (RA, liver cirrhosis)
	Coronary spasm	SVT		Diabetic ketoacidosis
	Hypercoagulable state	Extreme exercise		Scorpion toxin
	Aortic dissection	Increased sympathetic activity		
	Coronary dissection	Right ventricular failure (PE, ASD)		

AS=aortic stenosis, COPD=chronic obstructive pulmonary disease, CHF=chronic heart failure, RA=rheumatic arthritis, SVT=supraventricular tachycardia, PE=pulmonary embolism, ASD=atrial septal defect.

Bolesnici i metode

Retrospektivno su uzeti podatci iz medicinske dokumentacije i baze podataka u Kliničkom bolničkom centru (UHC) Zagreb za 2014. godinu. U ovo istraživanje uključeni su bolesnici kojima je 2014. godine, zbog sumnje na akutni koronarni sindrom (ACS), učinjena koronarna angiografija i koji su osjećali bol u prsnom košu uz pozitivan nalaz troponina.

Isključeni su svi bolesnici koji su imali suženje koronarne arterije veće od 30 %, kao i oni kojima je nedostajao podatak o vrijednosti troponina.

U bolesnika je provedena standardna procedura kakva se u UHC-u Zagreb rutinski provodi u evaluaciji bolesnika s bolom u prsima, a uobičajeno sadržava anamnezu, čimbenike rizika za aterosklerotsku CAD, laboratorijske nalaze, klinički pregled, EKG, ultrazvuk srca i koronarografiju. Uzeti su i podatci o laboratorijskim nalazima, kao što su troponin T, C-reaktivni protein, parametri funkcije bubrega (kreatinin) te kreatin kinaza (CK). Troponin je određen odmah pri prvoj prezentaciji i nakon toga serijski, a vršna je vrijednost uzeta kao referentna u ovom ispitivanju. Test visoko senzitivnog cTnT-a (hs-cTnT) bio je uporabljen u identifikaciji troponina u serumu. Riječ je o modificiranoj, četvrtoj generaciji testa, koji je signifikantno unaprijedio smanjenje lažno „pozitivnih" nalaza.[12] Porast troponina T definiran je kao veći od >0,014 ng/mL (14 ng/L) (granična vrijednost). Unutar 24 sata od prijema rutinski je određen CRP. Koncentracija >5 ng/mL smatrana je povišenom. Kreatinin je određen enzimskim kolorimetrijskim testom. Granična vrijednost za muškarce bila je 105 µmol/L, te 85 µmol/L za žene. Serumske vrijednosti CK mjerene su metodom enzimski katalizirane reakcije. Normalne su vrijednosti bile od 0 do 177 U/L. Aktivnost CK najviša je u skeletnoj muskulaturi, a slijede srčani mišić, mozak i ostala tkiva.[13]

Rezultati

U UHC-u Zagreb 2014. godine koronarna je angiografija provedena u 2433 bolesnika zbog različitih indikacija, koje su navedene u **tablici 2.** Indikacije odgovaraju opcijama ulaznih dijagnoza iz spomenute baze podataka Laboratorija za kateterizaciju (unesene su prije procedure), te, iako ima nekih preklapanja, navedena tablica daje dobar uvid o spektru razloga za koronarografiju 2014. godine.

Od ukupnoga broja od 2433 procedure, 947 (38,92 %) bolesnika imalo je troponin pozitivan „bol u prsima" i, u skladu s tim, sumnju na ACS. Od tih 947 bolesnika s ACS-om, 32 oboljela (3,38 %) imala su alternativni uzrok miokardne lezije. Prosječna vrijednost vršnog troponina u bolesnika bez ACS-a ili bez značajne CAD bila je 0,372 ng/L (raspon 0,02 – 3,48 ng/L). CRP je određen u 30/32 bolesnika i u 19 (63,33 %) njih bio je povišen (srednja vrijednost 26,1mg/L, raspon 5,13 – 115,2 mg/L). CK je mjeren u 30/32 bolesnika s urednom koronarografijom i bio je povišen u 12 bolesnika (40 %) (srednja vrijednost 281,7U/L, raspon 18 – 1921 U/L). Kreatinin je izmjeren u 29/32 bolesnika s normalnom koronarnom angiografijom (srednja vrijednost 127,6, raspon 39 – 629 umol/L).

Ispitivali smo i vodeći simptom u podskupini bolesnika s povišenim troponinom i normalnom koronarnom angiografijom. Bol u prsima klasificirali smo u tipičnu anginu, atipičnu i neanginoznu bol. Tipičan je anginozan bol retrosternalne lokacije, provociran tjelesnim naporom ili stresom, uz brzu re-

Evidence of elevated cTnT without the abovementioned additional criteria for MI should just be classified as myocardial injury. Myocardial injury can be the result of a number of other clinical scenarios with cardiac and non-cardiac etiologies[9-11], listed in **Table 1** and explained later.

Patients and Methods

Data were assessed retrospectively from medical files and databases collected in 2014 at the Zagreb University Hospital Centre (UHC). Patients included in this study were those who underwent coronary angiography in 2014 due to suspected acute coronary syndrome (ACS) and who had troponin-positive chest pain.

We excluded all patients that had coronary arterial luminal stenosis greater than 30% as well as patients with missing data on troponin concentrations.

The patients underwent the usual routine procedures of Zagreb UHC for assessment of patients with chest pain that usually included clinical history to also establish risk factors for atherosclerotic CAD, laboratory examination, physical examination, ECG, echocardiography, and coronary angiography. We also collected data on laboratory parameters such as troponin T, C-reactive protein, renal parameters (creatinine), and creatine kinase (CK). Troponin T was determined immediately and serially after the onset of pain, but peak Troponin T values were used for the purpose of this study. A high-sensitive cTnT (hs-cTnT) assay was used to detect the presence of troponin in serum. This assay is a modification of the fourth-generation cTnT assay and is significantly improved to further reduce the possibility of false "positive" findings[12]. Troponin T increase was defined as >0.014 ng/mL (14 ng/L) (cut-off value). Routine CRP was measured within 24 h from admission. A concentration of >5 ng/mL was considered elevated. Creatinine was determined by enzymatic colorimetric assay. Cut-off value for men was 105 µmol/L and 85 µmol/L for women. Serum values of creatine kinase were measured using an enzymatic rate method of foregoing reaction catalyzed by creatine kinase. The normal reference range was 0-177 U/L. Creatine kinase activities are greatest in skeletal muscles, followed by the heart, brain, and other tissues[13].

Results

In Zagreb UHC in 2014, a total of 2433 coronary angiography procedures were performed due to different indications that are listed in **Table 2**. Indications correspond to possible entry options from the catheterization laboratory database (entered before the procedure), and although there is some overlap present, the table gives an overview of the spectrum of reasons for coronary angiography in 2014 in Zagreb UHC.

Out of the total number of 2433 procedures, 947 (38.92%) patients had troponin-positive chest pain and were consequently suspected of having ACS. Of those 947 patients with suspected ACS, 32 (3.38%) had an alternative cause for myocyte injury. The average serum troponin T in patients without ACS or any other significant CAD was 0.372 ng/L (range 0.02-3.48ng/L). CRP was measured in 30/32 patients, and in 19 (63.33%) was found to be elevated (mean 26.1 mg/L, range 5.13-115.2 mg/L). CK was measured in 30/32 of patients with normal coronary angiography and was found to be elevated in 12 patients (40%) (mean 281.7 U/L, range 18-1921 U/L).

TABLE 2. Indications for coronary angiography in 2014 at the Zagreb University Hospital Centre.

Indications	% of patients (n=2433)	Indications	% of patients (n=2433)
Stable angina	564 (23.18)	Cardiac arrest	25 (1.03)
STEMI	336 (13.81)	Pre-transplantation evaluation	15 (0.62)
Unstable angina	314 (12.91)	Hypertrophic cardiomyopathy	13 (0.53)
NSTEMI	297 (12.21)	Aortic aneurysm	9 (0.37)
Elective PCI	280 (11.51)	Myocarditis	5 (0.21)
Ischemic heart disease screening	146 (6.00)	Cardiogenic shock	3 (0.12)
Valvular heart disease evaluation	103 (4.23)	Congenital Heart Disease	3 (0.12)
Cardiomyopathy screening	95 (3.90)	Endocarditis	3 (0.12)
Pre-operative evaluation	94 (3.86)	Pericarditis	3 (0.12)
Post-transplant evaluation	57 (2.34)	Pulmonary arterial hypertension	2 (0.08)
Rhythm abnormality	34 (1.40)	Explant preparation	1 (0.04)
Subacute myocardial infarction	31 (1.27)		

STEMI=acute myocardial infarction with ST-segment elevation, NSTEMI=acute myocardial infarction without ST-segment elevation, PCI= percutaneous coronary intervention.

gresiju mirovanjem ili primjenom nitroglicerina. Ako su dva od ovih obilježja bila prisutna, bol u prsima klasificiran je kao atipičan, dok je u prisutnosti samo jednog od tih obilježja, bol okarakteriziran kao neanginozan[12,14]. Klasifikacija bola prikazana je u **tablici 3.**

Ostale kliničke karakteristike bolesnika s troponin pozitivnim „bolom u prsima" prikazane su u **tablici 4**. Većina ih je imala kardiovaskularni rizik i komorbiditete, koji povećavaju mogućnost budućih kardiovaskularnih događaja (**tablica 5**). Kao najčešći uzroci identificirani su hipertenzivna bolest srca, Takotsubo sindrom i miokarditis (**tablica 6**).

Svi nalazi EKG-a prikazani su u **tablici 7**. Elevacija ST-segmenta bila je uobičajena u bolesnika s dijagnozom Takotsubo sindroma, dok su negativni T-valovi bili najčešći nalaz u bolesnika s hipertenzivnom krizom (**tablica 7**).

Rasprava

U ovom istraživanju 32 (3,38 %) bolesnika liječena u UHC-u Zagreb 2014. godine imala su troponin pozitivan bol u prsima, sumnju na ACS i nisu imali značajnu bolest koronarnih arterija, pa su stoga imali kriterije za miokardnu leziju ili MI tipa 2.

Više kardijalnih i nekardijalnih stanja opisano je kao uzrok porasta troponina u odsutnosti kriterija za dijagnozu MI-ja tip 1[5-7,15-24]. Mehanizam koji uzrokuje porast troponina ima i veliku terapijsku važnost. Koronarna angiografija možda nije prikladna metoda u nekih od tih bolesnika. Povišeni troponin u odsutnosti tipične prezentacije ACS-a dijagnostički je izazov, što je uočljivo i u našem istraživanju. Svi su bolesnici podvrgnuti koronarografiji, a poslije se pokazalo da su imali alternativne razloge za porast troponina. Troponin može porasti zbog nerazmjera između zahtjeva i opskrbe miokarda kisikom ili zbog izravnog oštećenja miokarda.

Creatinine was measured in 29/32 of the patients with normal coronary angiography (mean 127.6, range 39-629 µmol/L).

We have also analyszed the leading symptoms in the patient subgroup of increased troponin and normal coronary angiography. Chest pain can be further classified as typical, atypical, or non-anginal. Typical features of anginal chest pain are retrosternal location, provocation by activity or stress, and fast relief by rest or nitroglycerine administration. If two of these three features are present the chest pain is classified as atypical, while the chest pain is classified as non-anginal pain if only one of the features is present[12,14]. Classification of chest pain described in those patients is shown in **Table 3**.

Other clinical presentations found in patients with troponin-positive chest pain are shown in **Table 4**. The majority of patients with troponin-positive chest pain had cardiovascular risk factors and comorbidities that increase risk for further cardiovascular events (**Table 5**). The most common causes identified were hypertensive heart, Takotsubo syndrome, and myocarditis (**Table 6**).

All electrocardiogram findings in our subgroup of patients are shown in **Table 7**. ST-segment elevation was common in patients diagnosed with Takotsubo syndrome, while negative T waves were most commonly seen with hypertensive crisis (**Table 7**).

Discussion

In this study, 32 (3.38%) patients in 2014 at Zagreb UHC with troponin-positive chest pain and suspected ACS had no angiographically significant CAD, therefore fulfilling criteria for neither myocardial injury or type 2 MI.

Various cardiac and non-cardiac conditions have been described to cause the increase of troponin in the absence of criteria to clearly diagnose type 1 MI[5-7,15-24]. Mechanisms cau-

TABLE 3. Types of chest pain.

Type of chest pain	Number of patients (n=32)
Atypical	14/32
Typical	13/32
Non-anginal pain	5/32

TABLE 4. Clinical presentations of patients with elevated troponin and normal coronary angiography.

Clinical presentation	Number of patients (n=32)
Dyspnea	8/32
None	5/32
Fever	5/32
Nausea	4/32
Palpitations	3/32
Headache	2/32
Cough	2/32

TABLE 5. Comorbidities and risk factors.

Comorbidity	Number of patients (n=32)
Hypertension	23/32
Dyslipidemia	10/32
Smoking	10/32
Diabetes type 2	7/32
History of ACS	6/32
Obesity	5/32
Malignant disease	3/32
COPD	3/32
Permanent AF	2/32
CHF	1/32

ACS=acute coronary syndrome, COPD=chronic obstructive pulmonary disease, AF=atrial fibrillation, CHF=chronic heart failure.

Ireverzibilno oštećenje miocita može biti uzrok inicijalnog otpuštanja troponina iz citosola, za razliku od reverzibilnog oštećenja, koje uzrokuje povećanu propusnost membrane i izlazak slobodnoga razgrađenog troponina bez nekroze miocita[25]. Oba ova mehanizma pojavljuju se u različitim fazama miokarditisa. Za dijagnozu akutnog miokarditisa bolesnik mora imati povišen cTnT s različitom kliničkom prezentaci-

sing elevation of troponin are of major therapeutic importance. Coronary angiography may not be appropriate in some of these patients. Increased troponin and absence of typical presentation of ACS presents a diagnostic challenge, as shown by patients included in this study, who all underwent coronary angiography and were later shown to have an alternative etiology of elevated troponin. Troponin may rise as a result of

TABLE 6. The causes of elevated troponin in the study population.

Diagnosis	Number of patients (n=32)
Myocarditis	6/32
Hypertensive heart disease	6/32
Hypertensive crisis	5/32
Takotsubo syndrome	4/32
Dilated cardiomyopathy	2/32
SVT (including FA)	2/32
COPD exacerbation	1/32
Pancreatitis	1/32
Pneumonia	1/32
Acute pulmonary embolism	1/32
Lung cancer	1/32
Collagenosis	1/32
Chronic kidney disease	1/32

SVT=supraventricular tachycardia, AF=atrial fibrillation, COPD=chronic obstructive pulmonary disease.

Table 7. ECG findings.

ECG findings	Number of patients (n=32)
Normal ECG	17
ST-segment elelavation (more than 0.05 mV)	6
T wave inversion	5
Atrial fibrillation	2
Sinus tachycardia	2
ST denivelation	2
Voltage criteria for LVH	1
LBBB	1

LVH=left ventricle hypertrophy, LBBB=left bundle branch block.

jom, težinom srčanog popuštanja (od blagih simptoma do fulminante kliničke slike kardiogenog šoka).

U nekim je slučajevima u ovom istraživanju riječ bila o pravoj nekrozi miocita, povezanoj s povećanom potrebom za kisikom u nemogućnosti dostatne opskrbe[10]. Dobar je primjer za takav nerazmjer hipertrofija miokarda, u hipertenzivnoj bolesti srca, koja je uočena u većini promatranih bolesnika.[26,27] Ekstremni napor i oslobađanje katekolamina i neuropeptida povezanih sa stresom (najčešće u Takotsubo sindromu) također su dokumentirani uzroci ovoga stanja.[23,28]

Tahikardija može uzrokovati porast troponina jer smanjuje vrijeme raspoloživo za dijastoličku koronarnu opskrbu.[29] Dinamika ST-segmenta u vrijeme epizoda tahikardije nije nužmismatch between myocardial oxygen supply and demand or as a result of direct damage to the myocardium.

Irreversible myocyte injury can cause an initial release of cytosolic troponin, in contrast to reversible injury which causes release of factors which lead to increased permeability of the membrane and leakage of degraded free troponin without myocyte necrosis[25]. Both mechanisms may occur in different phases of myocarditis. For the diagnosis of acute myocarditis, the patient has to have elevated cTnT with varying severity of clinical presentation of acute heart failure (from no or mild symptoms to fulminant myocarditis causing cardiogenic shock).

Some cases in our study involved true myocyte necrosis that was related to increased oxygen demand in the absence

no rezultat ishemije[30]. Porast troponina te frekvencija i trajanje tahikardije nisu u ranijim istraživanjima pokazali jasnu povezanost[29,30].

Toksični citokini, apoptoza u tijeku, kronična ishemija i gubitak integriteta stanične membrane također mogu uzrokovati porast troponina u bolesnika sa srčanim popuštanjem[31,32]. Dodatno tomu pridonosi i stalan gubitak vijabilnih miocita, što je karakteristično za progresivno srčano popuštanje i objašnjava porast troponina.[33]

I u bolesnika s umjereno velikom, velikom ili masivnom plućnom embolijom primijećen je porast troponina. To može biti rezultat povećane potrebe za kisikom desne klijetke, a to pak uzrokuje desnostranu ventrikulsku dilataciju i ishemiju.[34]

U egzacerbaciji kronične opstruktivne plućne bolesti katkad se vidi istaknut upalni odgovor koji predisponira oštećenje miokarda.[35] U takvih je bolesnika porast troponina snažan prediktor bolničke smrtnosti.[36]

Smanjena koronarna rezerva zbog kombinacije hipertrofije klijetke, tahikardije i nižih tlakova punjenja koronarnih arterija, što možemo naći u bolesnika sa značajnom aortalnom stenozom, također mogu biti uzrok ishemije.[37]

Zaključak

Odsutnost angiografski značajne CAD u bolesnika koji zadovoljavaju kriterije za MI zahtijeva daljnja istraživanja etiologije miokardnog oštećenja u takvih bolesnika. Troponin nije toliko koristan za potvrdu dijagnoze ACS-a zbog svoje slabije specifičnosti koliko je senzitivan marker za isključenje infarkta bez ST-elevacije.

of an appropriate supply[10]. A good example of mismatch are hypertrophied hearts such as in hypertensive heart disease, which was observed in most of the patients reviewed[26,27]. Strenuous exercise, catecholamine release, and stress-related neuropeptides (the latter two most commonly seen in Takotsubo syndrome) are also documented causes[23,28].

Tachycardia can also result in an increase of troponin because there is decreased time available for diastolic coronary perfusion[29]. Alteration in the ST-segment during episodes of tachycardia is not necessarily an indication of the presence of ischemia[30]. Troponin elevation and the rate and duration of tachycardia, however, showed no relationship in previous studies[29,30].

Toxic cytokines, ongoing apoptosis, chronic ischemia, and loss of cellular membrane integrity can all cause elevation of troponin in patients with heart failure[31,32]. In addition, ongoing loss of viable cardiac myocytes, which is characteristic for progressive heart failure, explains elevation of troponin[33].

Elevation of troponin has been observed in patients with moderate-to-large pulmonary embolism or massive pulmonary embolism. It can be a result of an increase in right ventricular myocardial oxygen demand, which may lead to right ventricular dilation and ischemia[34].

Exaggerated inflammatory response, as seen in patients with chronic obstructive pulmonary disease (COPD) exacerbation, can also predispose for myocardial injury[35]. Elevated troponin is a strong predictor of in-hospital death in patients who are admitted for COPD exacerbation[36].

Ischemia can also be the result of impaired coronary flow reserve caused by a combination of ventricular hypertrophy, tachycardia, and lower perfusion pressure, all which can occur in patients with significant aortic stenosis[37].

Conclusion

Absence of angiographically significant CAD in patients with criteria for MI warrants further investigation on the etiology of myocardial injury in those patients. Troponin is not so useful to "rule in" ACS due to its lack of specificity, but it is a sensitive biomarker to "rule out" non-ST-segment elevation myocardial infarction.

LITERATURE

1. Collinson PO, Boa FG, Gaze DC. Measurement of cardiac troponins. Ann Clin Biochem. 2001 Sep;38(Pt 5):423-49. https://doi.org/10.1177/000456320103800501
2. Antman EM. Decision making with cardiac troponin tests. N Engl J Med. 2002 Jun 27;346(26):2079-82. https://doi.org/10.1056/NEJMe020049
3. Christenson RH; National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Utilization of Biochemical Markers in Acute Coronary Syndromes and Heart Failure. Clin Chem. 2007 Apr;53(4):545-6. https://doi.org/10.1373/clinchem.2006.079749
4. Zimmerman J, Fromm R, Meyer D, Boudreaux A, Wun C, Smalling R, et al. Diagnostic Marker Cooperative Study for the Diagnosis of Myocardial Infarction. Circulation. 1999 Apr 6;99(13):1671-7. https://doi.org/10.1161/01.CIR.99.13.1671
5. Mahajan N, Mehta Y, Rose M, Shani J, Lichstein E. Elevated troponin level is not synonymous with myocardial infarction. Int J Cardiol. 2006 Aug 28;111(3):442-9. https://doi.org/10.1016/j.ijcard.2005.08.029
6. Nageh T, Sherwood RA, Wainwright RJ, Shah AM, Thomas MR. The clinical relevance of raised cardiac troponin I in the absence of significant angiographic coronary artery disease. Int J Cardiol. 2005 Apr 20;100(2):325-30. https://doi.org/10.1016/j.ijcard.2005.01.001
7. Lai H, Patil A, Aronow W, Alexa M Wa Li Y, Jesmajain S. Causes of Increased Cardiac Troponin I Levels in Hospitalized Patients Without Coronary Artery Disease. Chest. 2011;140(4_Meeting Abstracts):985A. https://doi.org/10.1378/chest.1100432
8. Thygesen K, Alpert JS, Jaffe AS, Chatiman BR, Bax JJ, Morrow DA, et al; ESC Scientific Document Group. Fourth Universal Definition of Myocardial Infarction (2018). Eur Heart J. 2019 Jan 14;40(3):237-269. https://doi.org/10.1093/eurheartj/ehy462
9. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol. 2003 Jun 4;41(11):2004-9. https://doi.org/10.1016/S0735-1097(03)00421-2
10. Burness CE, Beacock D, Channer KS. Pitfalls and problems of relying on serum troponin. QJM. 2005 May;98(5):365-71. https://doi.org/10.1093/qjmed/hci055

11. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. Ann Intern Med. 2005 May 3;142(9):786-91. https://doi.org/10.7326/0003-4819-142-9-200505030-00015
12. Borg G, Lindblad I, Holmgren A. Quantitative evaluation of chest pain. Acta Med Scand Suppl. 1981;644:43-5. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/6941642
13. Glynn M, Drake W, Hutchison R, eds. Hutchison's clinical methods. Edinburgh: Elsevier; 2012.
14. Gibbons RJ, Chatterjee K, Daley J, Douglas J, Fihn S, Gardin J, et al. ACC/AHA/ACP ASIM Guidelines for the Management of Patients With Chronic Stable Angina: Executive Summary and Recommendations : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). Circulation. 1999 Jun 1;99(21):2829-48. https://doi.org/10.1161/01.CIR.99.21.2829
15. Sybrandy KC, Cramer MJ, Burgersdijk C. Diagnosing cardiac contusion: old wisdom and new insights. Heart. 2003 May;89(5):485-9. https://doi.org/10.1136/heart.89.5.485
16. Hein S, Scheffold T, Schaper J. Ischemia induces early changes to cytoskeletal and contractile proteins in diseased human myocardium. J Thorac Cardiovasc Surg. 1995 Jul;110(1):89-98. https://doi.org/10.1016/S0022-5223(05)80013-3
17. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation. 2003 Aug 19;108(7):833-8. https://doi.org/10.1161/01.CIR.0000084543.79097.34
18. Logeart D, Beyne P, Cusson C, Tokmakova M, Leban M, Guiti C, et al Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. Am Heart J. 2001 Feb;141(2):247-53. https://doi.org/10.1067/mhj.2001.111767
19. Ben Yedder N, Roux J, Paredes F. Troponin elevation in supraventricular tachycardia: primary dependence on heart rate. Can J Cardiol. 2011 Jan-Feb;27(1):105-9. https://doi.org/10.1016/j.cjca.2010.12.004
20. Carlsson J, Brockmeier J, Cuneo A, Tebbe U. Elevation of cardiac troponin after sustained tachycardia is a frequent finding in patients without evidence of acute coronary disease. EP Europace. 2003;(4 Suppl_2):B174. https://doi.org/10.1016/eupace/4.Supplement_2.B174
21. Lum G, Solarz DE, Farney L. False Positive Cardiac Troponin Results in Patients Without Acute Myocardial Infarction. Lab Med. 2006 Sep;37(9):546-550. https://doi.org/10.1309/T94UUXTJ3TX5Y9W2
22. Lauer MS. Cardiac troponins and renal failure: the evolution of a clinical test. Circulation. 2005 Nov 15;112(20):3036-7. https://doi.org/10.1161/CIRCULATIONAHA.105.579888
23. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation. 2008 Dec 16;118(25):2754-62. https://doi.org/10.1161/CIRCULATIONAHA.108.767012
24. Alegría-Ezquerra E, González-Juanatey J, González-Maqueda I. [Hypertensive heart disease: a proposed clinical classification]. Rev Esp Cardiol. 2006 Apr;59(4):398-9. https://doi.org/10.1157/13087067
25. Afonso L, Bandaru H, Rathod A, Badheka A, Ali Kizilbash M, Zmily H, et al. Prevalence, determinants, and clinical significance of cardiac troponin-I elevation in individuals admitted for a hypertensive emergency. J Clin Hypertens (Greenwich). 2011 Aug;13(8):551-6. https://doi.org/10.1111/j.1751-7176.2011.00476.x
26. Vidt DG. Hypertensive crises: emergencies and urgencies. J Clin Hypertens (Greenwich). 2004 Sep;6(9):520-5. https://doi.org/10.1111/j.1524-6175.2004.03607.x
27. Ammann P, Fehr T, Minder EI, Günter C, Bertel O. Elevation of troponin I in sepsis and septic shock. Intensive Care Med. 2001 Jun;27(6):965-9. https://doi.org/10.1007/s001340100920
28. O'Hanlon R, Wilson M, Wage R, Smith G, Alpendurada FD, Wong J, et al. Troponin release following endurance exercise: is inflammation the cause? a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson. 2010 Jul 2;12:38. https://doi.org/10.1186/1532-429X-12-38
29. Xue F, Jiang TB, Jiang B, Cheng XJ, He YM, Li X, et al. Cardiac troponin I elevation with supraventricular tachycardia: two case reports and review of the literature. BMC Res Notes. 2014 Mar 11;7:136. https://doi.org/10.1186/1756-0500-7-136
30. Coppola G, Carità P, Corrado E, Borrelli A, Rotolo A, Guglielmo M, et al; Italian Study Group of Cardiovascular Emergencies of the Italian Society of Cardiology. ST segment elevations: always a marker of acute myocardial infarction? Indian Heart J. 2013 Jul-Aug;65(4):412-23. https://doi.org/10.1016/j.ihj.2013.06.013
31. Wencker D, Chandra M, Nguyen K, Miao W, Garantziotis S, Factor SM, et al. A mechanistic role for cardiac myocyte apoptosis in heart failure. J Clin Invest. 2003 May;111(10):1497-504. https://doi.org/10.1172/JCI17664
32. Foo RS, Mani K, Kitsis RN. Death begets failure in the heart. J Clin Invest. 2005 Mar;115(3):565-71. https://doi.org/10.1172/JCI24569
33. Davies CH, Harding SE, Poole-Wilson PA. Cellular mechanisms of contractile dysfunction in human heart failure. Eur Heart J. 1996 Feb;17(2):189-98. https://doi.org/10.1093/oxfordjournals.eurheartj.a014834
34. Irwin RS, Rippe JM. Irwin and Rippe's Intensive Care Medicine. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
35. Søyseth V, Bhatnagar R, Holmedahl NH, Neukamm A, Høiseth AD, Hagve TA, et al. Acute exacerbation of COPD is associated with fourfold elevation of cardiac troponin T. Heart. 2013 Jan;99(2):122-6. https://doi.org/10.1136/heartjnl-2012-302685
36. Noorain S. Prognostic value of cardiac troponin I during acute exacerbation of chronic obstructive pulmonary disease: A prospective study. Lung India. 2016 Jan-Feb;33(1):53-7. https://doi.org/10.4103/0970-2113.173052
37. Nunes JP. Elevated troponin and aortic valve disease. J Am Coll Cardiol. 2013 Apr 2;61(13):1467. https://doi.org/10.1016/j.jacc.2012.11.069